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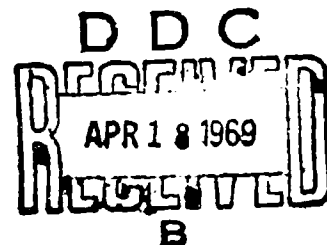
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DEPARTMENT OF THE ARMY
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Title: Investigations on a flaps*-like disease of cattle ("benign flaps",
stomatitis papulosa bovis specifica). (Untersuchungen über eine
maulseuchehochliche* Erkrankung des Rindes ("gutartige Maulseuche",
Stomatitis papulosa bovis specifica)).

Journal: Z. Infekt. Hyg. Haustiere 1: 3-20 (1906).

* "Maulseuche", literally translated, means "mouth disease". An old German-
English dictionary printed about the same year as this paper gave the
translation "flaps", a term used in veterinary medicine.

February 1969

In the spring of 1904, when bavarian beef was moved from rich pasture lands to the cattle yard for sale, an infection, which reached epidemic proportions and affected the mucous membranes of the mouth, was observed among the cattle. The disease spread quickly among those animals which had been in contact with the bavarian cattle. The disease aroused very great interest since its symptoms were easily confused with those of foot-and-mouth disease. Through the cordial intervention of Dr. Arnt, Veterinary Surgeon, and the willingness of the management of the cattle yards, on 6 May 1904, we were able to obtain an animal which was still sick for use in our studies. This animal served as the source of material for all our later studies.

Findings in The Case of Spontaneously Ill Cattle

The steer was five years old and in good health from a nutritional point of view. The general state of health had not been impaired. In particular, there was no elevation of the body temperature (39°C) as a result of fever. The animal consumed the hay that was made available to it with a good appetite. Salivation persisted both before introduction and during eating.

Local conditions: upon opening the oral cavity, one observed on the front side of the hard palate, many lentil- to five-pfennig*-sized area with fairly well defined edges. These were rather prominent over the whole area. The foci were separated from the healthy tissue by a narrow, ca. $1-1\frac{1}{2}$ mm wide, grey-red zone which gradually changed to red in color as it approached the inner area. In their centers, the areas exhibited a yellowish-grey, thick, partly finely and partly coarsely granulated, torn, surface area. The yellowish-grey mass was stuck solidly to the underlying layer of tissue and could be neither removed like a membrane nor otherwise easily removed. Several such areas of lentil to pfennig size

* A "pfennig" is a german coin.

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...the mucous membrane of the cheek in every case. In addition, various oval-shaped foci of 1-1½ cm in diameter were found on the mucous membrane of the underside of the tongue near to the frenulum of the tongue. With the exception of their size, these foci were identical to the disease foci already described with regards to their characteristics (see the table at the end of this number (issue) of the Journal).

Transmission Studies With Treated Pieces

The investigation of the food, the water, and the stable yielded no support for the hypothesis that the appearance of the disease was the result of the presence of a physical or chemical noxious agent. Rather, it was concluded that the disease developed after the exposure of the subject to another diseased animal. In order to obtain this evidence, from the diseased cattle, three foci present on the underside of the tongue were excised along with a small portion of normal tissue and were employed for the transmission studies that were carried out using calves and older cattle at the Hygienic Institute. A portion of the materials was preserved immediately after removal in formalin and concentrated sublimate solution for later histological examinations.

The excised mucous membranes were inoculated into five calves which had been in the study stables of the Hygienic Institute since autumn of 1903. Transmission occurred via the mucous membrane material and was carried out in the following manner: the tongue was drawn out of the mouth; hereupon, the mucous membrane near the frenulum of the tongue was pierced with a pair of scissors and with the point of the closed scissors, a 1-2 cm-deep incision was made.

In such pockets as these, a particle of the mucous membrane from the sick animal was enclosed and the inoculation was sealed by simultaneously passing a wire through the edge of the pocket and the inserted material.

After two to four days in all the calves thus inoculated, a strong to weak reddening and swelling occurred at the site of inoculation. After six to seven days, however, these symptoms of inflammation gradually receded in the area of the wound. Up to the twelfth day after inoculation, no suspicious lesions were observed in the oral cavities of any of the experimental animals. In addition, none of the animals exhibited a diminished appetite, decrease in weight, or change in body temperature. Suddenly, on the thirteenth day after inoculation, there appeared at the site of the inoculation, small, dispersed, red spots.

Findings By Inoculation

Calf No. 1, male 3/4 years old, red and white, in a reasonably good state of health. On 20 May, 14 days after transmission of the inoculum to this calf, six mustard seed to lentil-sized areas were visible on the bottom of the tongue at various distances from the site of inoculation. Additional areas with the same appearance were found near the first molar tooth and on the inner side of the lower lip. The surface of the small spots was smooth, while the larger ones exhibited a light granulation in the center. Upon more precise inspection, it could be seen that in the middle of these areas, there was the loss of substance such as would be found if someone had used a hole cutter. The center of the spots lay, therefore, about $\frac{1}{2}$ to $\frac{1}{4}$ mm below the level of the inflamed adjacent tissue of the infected area and was surrounded by steep walls. The centers of larger spots had a grey-red color and a granular appearance. After two days, the foci had attained the size of a pfennig-piece or larger. Their centers assumed a yellowish-grey color and after two more days, two of the foci had achieved the size of a 10-pfennig piece and had grey-yellow, broken centers. Between the sixth and eighth days, the red borders around most of the round disease foci appeared to fade, and in their place, a patch of smooth, dull-red

epithelium began to form. This soon reached the healthy mucous membrane on one side so that the disease foci frequently assumed a crescent shape after some time. From the yellow-red patches as well as at the borders, the formation of new epithelium advanced rapidly. As a result, fourteen days after formation of the first, the diseased area could be differentiated from healthy mucous membrane only by a mild reddening and swelling. The last remnants of the disease, however, were still detectable up to two months after the onset of the first symptoms. Later, this calf was infected once more. During an inspection, which was carried out three months after the first transmission study, we found in the oral cavity, the lips, the hard palate, the cheeks, and the tongue areas of infection like those already described. These lesions receded quickly but new lesions appeared. The result was that the animal exhibited forms of mild lesions in various stages of development for several months after infection.

Calf No. II, male, red-white, 3/4 years old, in good state of health. On 20 May, on this animal were observed on the underside of the tongue, three lintel-sized, grey-red, sharply circumscribed areas with red borders of $1\frac{1}{2}$ mm thickness. The lesions were prominent on the surface and had partially divided centers. One on the toothless edge of the intermaxillary bone and the first molar tooth, the other two on the inner side of the lower lip. The third calf exhibited four lintel-sized, greyish-red, somewhat raised patches. These did not spread any further but did develop a greyish-yellow surface, which subsequently turned to a yellow color and became lumpy. By 28 May, their presence was detectable only through a diffuse reddening. On 20 May, several lintel-sized foci were found on the inner side of the lower lip across from the left maxilla. In a similar area on the upper lip was noticed a grey-yellow lesion about the size of a five pfennig piece. During this expansion, the infection spread to the connective tissue of the lip. After this, firstly, the area and

folds of the mucous membrane of the lips disappeared. The infected part was raised above the background by about 1 mm and assumed a gray-red color. Up to now, the surface had been uniform. After two days, the inner area of the patch contrasted sharply with the surrounding border. The color gradually assumed a gray, gray-yellow, and dirty yellow tone. Repeatedly, there now formed from the center a trail across the healthy, surrounding mucous membrane, and in this way, the crescent form on the mucous membrane was produced. However, healing frequently occurred simultaneously from within and without. On the mucous membrane of the lower lip laying near the maxilla, the healing process proceeded much slower than was observed elsewhere. The tessellation of the connective tissue of the lips was still missing after sloughing off of the yellow mass. The newly formed epithelium at this site was originally thickened and after several weeks, the first sulcus formation appeared.

After the process at the area mentioned had formed again, the mucous membrane in the area of the sublingual caruncle became infected. In this case, the lesions on the mucous membrane assumed irregular shapes, and the healing-up process proceeded much more slowly. This was accomplished a month longer than with the previous area. The healing process began in the middle as well as at the edges.

On 24 May, in the lower, inner corner of the right nostril, a light circumscribed reddening appeared. In the days that followed, the center became grey, assumed the size a ten pfennig piece, and later exhibited a more grey-yellow coloration. Also, at the beginning, the area and folds of the muzzle were swollen and indistinct. Healing commenced simultaneously at both the middle and the edges; after new formation of epithelium, the area was raised up above the surface by its thickness and still showed for some time longer a color inclined to yellow. After even a longer time, the folds also reappeared. The disease did not appear to produce any lesions on the epithelium of the muzzle glands, however, this area was dry during the illness.

In the case of Colt No. II, the lesions that occurred as a result of inoculation suddenly disappeared almost completely. However, a relapse occurred and lesions appeared on the mucous membrane of the oral cavity, but in a milder form. The recovery now proceeded slowly and when it was complete, a third infectious process appeared.

Upon destruction of the animal in the middle of July, numerous affected areas on the upper and lower lips, on the hard palate, on the underside of the tongue, and on the muzzle were found. In addition, on the soft palate and on the side of the mouth, two areas with greyish-yellow, torn centers and red margins were observed. Also, there were similar areas observed in the throat. Analogous lesions were absent from the stomach and intestine as shown by the post-mortem examinations.

Colt No. III, black-white, male, 3/4 years old, very good health. On 20 May, four dirty yellow-grey, sharply circumscribed patches were found on the muzzle below the nostrils. These stood out prominently against the surrounding tissues. In the middle of the lower lip was found a 2 cm-wide, round lesion which was recognizable by three, differently colored, concentric rings. The outermost ring was dark-grey; the second was tinted slightly yellow; and the central ring was yellow-grey. The area was prominent on the surface and was 1 mm thick. 1 1/2 cm from the right corner of the mouth, a lesion was found on both the upper and lower lips. These lesions were on the connective tissue and stood about 3 mm above the normal, surrounding tissue. In the left corner of the mouth were found similar lesions. The lesion on the upper lip was the size of a ten pfennig piece while the one on the lower lip was pencil-sized. In all these areas, a characteristic dryness was noticeable. On the toothless area of the jaw were found several hempseed-sized lesions which were surrounded by bluish-red zones and were rather noticeable. These

were each about 2 cm from the center. Slightly further removed from the center on the left side, another similar area was present. In this case, the center lay 3 mm below the nasal neighboring tissues thus giving the appearance of a crater-like lesion with steep walls. The area had a grey-red color and a granulated surface. On the inside of the upper lip on the mucous membrane at those places where the three first incisions came to rest, were found three lintel-sized, yellowish-grey, sharply circumscribed lesions, which were surrounded by a reddened zone. The interiors of the foci were separated from the swollen mucous membrane by steep walls and had a granulated appearance. At the edge of the hard palate near to the soft palate were found 40 to 50, 1-3 mm-sized, sharply circumscribed, red patches which were slightly raised above the surrounding tissue. It was noted that these lesions in particular were present on the fimbriated borders. On the underside of the tongue and on the frenulum were found twelve of the areas described above. In a few days, these attained the size of a ten pfenning piece and by that time, a yellowish, segmented center and a raised, reddish peripheral zone could be seen. The site of inoculation was 3 cm long, 1½ cm wide, and had swollen, yellowish edges.

The lesions on the mucous membrane were distinguished by their size and depth. Particularly severe were the lesions on the inside of the lower lip and on that area of the mucous membrane in contact with the incisors. Individual lesions located on the hard palate reached the size of a mark-piece in a few days. During the course of the illness, there was a very conspicuous sweetish odor from the oral cavity which persisted for a long time. In the case of Calf No. III, the process of healing took a long time in spite of the fact that it began at the centers as well as along the edges. Because of the new lesions, the illness persisted until October.

Each of the previously mentioned calves (Nos. IV and V) were sick on 20 May but had only a few infected area in the region of the edges of the hard palate and on the under side of the tongue. These healed again quickly.

On 21 May 1904, three more calves (Nos. VI, VII, and VIII) were inoculated with material from calves Nos. I, II, and III. These animals became ill within 24 hours and, for the most part, exhibited symptoms which were the same as those observed in Calves Nos. I-III. Also, in the case of calves VI through VIII, relapses occurred frequently.

Through these studies it was proven that the illness under discussion here is a contagious disease.

Transmission Studies with Blood

In the case of the five calves which were inoculated on 6 May 1904, with material originating from spontaneously sick steers, lesions appeared which were similar to those observed with the three later study animals. At the first inoculation of calves Nos. I - IV on 20 May, it was noted that the lesions did not develop at the site of inoculation but on the mucous membrane nearest to it in the oral cavity. Then suddenly, much different areas of the oral cavity were attacked. From these sudden and unpredictable appearance of the lesions of the disease, it could be concluded that the agent of the disease, in a way similar to the agent of hoof- and - mouth disease, was carried in the blood stream.

In order to determine whether or not this was the case, transmission studies using the transfusion of blood from infected calves to healthy calves was carried out. A bacteriological study of the blood was also performed. On 21 May, on the day after the onset of the first symptoms in Calves Nos. I-IV, from calf No. III, which showed the severest lesions, blood was removed with a sterile syringe. 10 cc of this blood was injected into Calf No. IX intravenously and 10 cc into

Calf No. X subcutaneously. On 23 May in the case of Calf No. IX and on 24 May in the case of Calf No. X (this is 2-3 days after inoculation with blood), symptoms of the illness appeared. We must emphasize, however, that in the case of Calves Nos. IX and X, the accidental transmission of the disease from Calves Nos. I-V cannot be excluded completely since they were taken care of by the same attendant as Calves I-V. He had fed the calves infected with blood first and then disinfected himself before feeding Calves Nos. I-V. In spite of this, the possibility still remains that Calves IX and X were not infected by the blood inoculation but rather accidentally by disease products from the mouths of calves Nos. I-V. The appearance of the disease in Calves IX and X was quite similar to that described for Calves Nos. I-III.

In the case of Calf No. IX (intravenous), on 23 May the muzzle appeared to be the chief area concerned. Particularly on the lower half of the nostril were found numerous poppy-seed-sized round patches which were slightly raised, lightly granulated, and appeared to be opaque. Their centers were sunken. They were bordered by steep walls and lay about $1/3$ mm below the normal surrounding tissue. The unaffected zone surrounding these areas had a gloss and was colored somewhat darker than the dark grey pigmented muzzle. By 24 May, the finely granulated patches under the surface had increased in size so that the largest had almost reached the size of a hempseed. Also, along the forward edge, several diffuse red areas were visible. During the next few days, numerous red patches developed on the mucous membrane of the intermaxillary bone. These had a dirty yellow-grey color and an uneven, shredded surface. Between the 26th and 27th, these poppy- to hempseed-sized patches were visible on the lower lip. The areas surrounding them were somewhat swollen. The disease foci lay $1/2$ mm below the surface, had steep walls, and were finely granulated. At these areas on the lips and muzzle, the lamination was lost. Also, the nodules in the folds of the muzzle

did not secrete any mucus. The first area on the muzzle to show signs of infection was in the mucosa covered with epithelium for the most part. However, swelling and dark discoloration of the area persisted for several more days. Also, the tevelation could not be distinctly seen for several more weeks. The muzzle glands began secreting again only after new epithelium had been formed and the swelling had subsided.

On the lower lip and on the lateral surface of the tongue, only mild lesions appeared. In the case of Calf X, several of the foci described earlier were observed on the muzzle. By 25 May, these had achieved the size of a 20-pfennig piece and had a dirty yellow color and a rough, dull surface. Healing of the lesions on the mucous membrane of the mouth occurred quite rapidly. A few insignificant lesions were found to reappear on the lower lip again.

On the skin of calves Nos. IX and X, after injection, dirty, grey-brown scabs were observed on the skin of calves Nos. IX and X. After a week, these disappeared again. These scabs were first observed in the case of calves Nos. IX and X. Later, they were observed also with other study animals. As a result, it has been assumed that they are symptoms of the disease syndrome.

Infection Studies with Blood Serum

For the further establishment of the role that blood plays as a carrier of the infectious agent of this disease, blood was withdrawn from Calf No. IX on 23 May. Part of the blood was employed for inoculation of culture media while the remainder was held in the refrigerator for serum production. The blood was examined in smears, preparations and in hanging drop preparations and was inoculated into all of the media available (agar, glycerin agar, blood agar, blood serum, serum agar, broth, serum broth, sugar broth, glycerin broth, and potatoes). The results of the microscopic and cultural studies were negative. Similar results had been obtained with the tests that were performed on the blood from spontaneously ill steers and on calves Nos. I to VIII.

On 24 May, abundant quantities of serum were obtained from the blood that had been held in the refrigerator. This was filtered through a Chamberland candle filter; the filtrate was free from visible and cultivatable microorganisms. Within 24 hours, 4 cc and 6 cc quantities were injected subcutaneously into Calves Nos. XI and XII respectively. Both of these calves were kept in a special stall and were cared for by a special attendant. On 8 June, Calf No. XII became ill and exhibited numerous lesions in the regions of the muzzle and the mouth. At the time the animal was slaughtered on 26 June, near the lesions on the muzzle and mouth, three lintel-sized areas with dull centers and segmented surfaces were found on the mucous membrane of the esophagus. The stomach and intestine of this animal, however, did not exhibit any lesions. Calf No. XI did not become ill.

Since in the study of the transmission of the disease via blood in the case of calves Nos. IX and X, another possible means of infection other than through the injected blood cannot be completely ruled out with certainty, two additional calves, Nos. XIII and XIV, were infected subcutaneously and intravenously on 12 June with blood from Calf No. XII. The calves were kept in a separate building and were taken care of by an attendant who had not previously come in contact with the study animals. Calf No. XIII had received 6 cc of blood subcutaneously while Calf No. XIV received 8 cc intravenously. Calf No. XIII became ill on 28 June and Calf No. XIV on 26 June. Both showed symptoms similar to those observed with Calf No. III.

In the case of calves Nos. XIII and XIV, it was noted that for about 7 to 8 days after appearance of the disease, suspicious lesions on the mucous membrane of the mouth were observed which disappeared again within 24 hours. Relapses occurred in these animals and noticeable lesions were still being observed in October of 1904.

The transmission studies that were carried out showed the possibility of transmission not only by products of the disease but also by blood and filtered blood serum. During the transmission studies with products of the disease and with blood, all of the study animals developed the illness. On the other hand, only one of the two animals injected with blood serum became ill. The appearance of the disease occurred after incubation periods of various lengths. In the case of the native material, the first symptoms appeared after 14 days. With material from the second generation, the symptoms appeared in 13 to 15 days. With intravenous and subcutaneous injections, in one case they appeared after 2 to 3 days, while in another case after 14 to 16 days. In the case of the transmission studies with serum, the symptoms appeared after 15 days.

For the purpose of obtaining additional information on the infectiousness of blood and unfiltered, as well as filtered serum, twelve additional cattle were obtained and were kept available at another site. These cattle ranged in age from 1½ to 2 years.

The materials for these additional transmission studies was obtained from Calf No. XIV. On 8 July 1904, when severe lesions appeared in this calf's mouth, blood was removed from the animal. A fraction of the blood was defibrinated while the remainder was refrigerated for serum production.

Of the twelve animals placed at our disposal, eight (in pairs) were placed in the four corners of a large, spacious stall located at the Veterinary High School. In the corners diagonal to each other with found the animals designated as Nos. XV, XVI, XVII, and XVIII. Nos. XV and XVI were free while Nos. XVII and XVIII were kept together. Cattle Nos. XV-XVIII served as study animals while the remaining animals (XIX-XXII) served as controls. On 9 July, Nos. XV and XVI each received subcutaneously 4 cc of unfiltered blood serum, while Nos. XVII and XVIII received 10 cc and 4 cc of defibrinated blood respectively. The defibrinated blood was infected contained a small amount of red blood cells.

At the first inspection on 16 July, typical diseased areas were observed on the mucous membrane of the oral cavities of Nos. XVII and XVIII. These, however, had disappeared by the time of the next examination on 19 July. The disease foci were found especially on the edges of the gums and on the inside of the lower lip. When the animals were re-examined on 24 and 25 July, alterations were no longer noticeable. For the first time on 9 August 1904, in the case of animals Nos. XVII and XVIII, diseased areas ranging up to the size of a ten pfennig piece were present on the edge of the hard palate as well as on the mucous membrane of the lower lip and tongue. In the case of animal No. XVII, a light scab formation on the skin was also observed. This disappeared several days later.

In the case of the animals injected with serum and with the control animals, no suspicious lesions in the oral cavity were observed during the specified period of observation. As a result, these animals were later re-employed in other experiments.

These studies show that infection can be accomplished by means of injections of defibrinated blood whereas the injection of blood serum does not appear to lead to any infection.

In the last study carried out by us, blood was removed from animal No. XVII on 9 August 1904. 20 cc of the separated serum were filtered through a Chamberland candle filter. The filtrate, like the blood from which it was derived, appeared to be free from detectable microorganisms. On 10 August 1904, 10 cc of the serum were injected into animals Nos. XXIII and XXIV. Unfiltered serum was injected into animals Nos. XXV and XXVI.

During a month-long observation period, these animals did not become ill. After that time, we did not have the opportunity to observe the animals again.

The results of the transmission studies with blood serum, which were carried out on cattle Nos. XV through XXVI, did not correlate exactly with the earlier studies. All of the cattle, which were injected with untreated blood taken from

the vein, became ill. In contrast, of the two calves (Nos. XI and XII), which were injected with filtered blood serum, only one (Nos. XII) became ill. Of the young steers Nos. XV and XVI, which were injected with unfiltered serum and animals Nos. XVII - XXVI, which were injected with unfiltered and filtered serum, none became ill. Based on the positive transmission attempt with one calf using filtered serum, it can be concluded that the virus responsible for the disease process in question here is filterable. The only interpretation of the negative results, however, is that the blood serum of the ill animal does not always contain the infectious virus. This conclusion is supported strongly by the studies with cattle Nos. XV-XXVIII. In this study, those animals injected with defibrinated blood became ill whereas the animals injected with serum prepared from the same blood remained healthy. Our conclusion is tentatively based on the varying behavior of blood serum obtained from diseased animals.

In the case of the evaluation of the results obtained from transmission studies, one must take into consideration the fact that older animals are more difficult to infect than younger ones as a general rule. In the case of two cows, 6 and 9 years old, we were successful in infecting them only after a second attempt using virus material implanted in the mucous membrane of the oral cavity. The infections that were induced were quite light. In the case of a three year old bull, a triple injection of the virus material employed with the cows did not give any positive results. The animals which were made available to us at another site ranged in age from $1\frac{1}{2}$ to 2 years. The calves used in the first study ranged from $\frac{1}{2}$ to 1 year old at the most.

It should be pointed out that the disease process in all of the animals was restricted to the mucous membrane of the oral cavity and the muzzle and that only in a few animals was scab formation on the skin observed. Upon dissection of

study animal No. XII, alterations on the mucous membrane of the esophagus were also found. On the other hand, in no cases were lesions in the area of the nasal mucous membrane, the conjunctiva of the eye, or, in the case of female animals, on the mucous membrane of the vagina ever observed. Even when infectious materials were transferred from the oral cavity of infected animals to the areas just mentioned, these areas did not produce lesions.

Spontaneous Transmission of The Disease

In the stall at the Hygienic Institute, in which the first five calves infected apt, five additional, uninfected calves were also kept. Of the latter, two became ill at the end of June and two more in the beginning of July 1904. From this, it can be concluded that spontaneously transmission of the disease from animal to animal can occur.

Nature of The Infectious Agent

During the description of the transmission studies, it was already pointed out that it was not possible to detect microorganisms in the blood used to elicit the disease. As a result, it can be concluded that the causative agent is neither a protozoan nor a bacterium. Since in one case, transmission of the disease was successfully carried out using a filtered blood serum, the infectious agent must be classified as filterable and ultraviable like the infectious agents of foot-and-mouth disease, fowl plague, and chicken pox.

In sections through diseased mucous membrane areas were found bacteria of various shapes and sizes. This would not have been expected based on the previous conclusions. Control studies with healthy animals, however, showed that these bacteria belonged to the flora normally associated with the mucous membrane of healthy cattle.

Histology of The Lesions on The Mucous Membranes

During the early stages of the disease, the mucous membrane is distinguished macroscopically by its strong inflammation, swelling, and by a yellowish color. From perpendicular sections through the mucous membrane, which have been stained with hematoxylin-eosin, methylene blue, and fuchsin, one can observe at the diseased area the following: the epithelial layer is significantly dispersed; the papillae are increased in size and length; in the layers of the mucosa lying below the epithelium, the blood vessels are fully swollen; and there are numerous white blood cells present in the area of the mucosa. If the individual cross-sections are examined closely, the cells of the connective tissue of the mucosa are found to be pushed apart and abundant numbers of white blood cells are present in the interstitial areas. The vessels are completely filled with red and white blood cells and are surrounded by a layer of white blood cells. The border between the mucosa and the epithelium of the Stratum cylindricum is indistinct. Between these tubule epithelia and the cells of the Stratum germinativum situated above it, numerous multi-nucleated leucocytes were found. The cells of the Stratum germinativum exhibit mostly small, unstained areas which have increased in size and number as compared to those of the Stratum granulosum. These are invariably found in the Stratum granulosum cells. The Stratum lucidum and corneum is present, however, as a homogenous layer.

In the second stage, during which the epithelial layer over the center of the diseased area has lifted off, one finds papillae which have only a small epithelial layer. Sometimes the papillae themselves are damaged at the top. The red margin surrounding the epithelial defect of the diseased area is distinguished by a strong vacuole formation in the cells of the Stratum germinativum. The Stratum corneum here has partially disappeared. The papillae and the mucosa show alterations similar to those described for the earlier stage.

The third stage is distinguished by a marked decrease of white blood cells in the mucosa and papillae as well as a decrease in the transverse lines of the papillae. On the other hand, the papillae have been noticeably increased in length. As a result, the epithelial tissues between papillae appear as narrow ridges. The newly formed epithelial layer at the base of the cavity gives the appearance of a railing in which one can differentiate bars and free panels. The bars can be regarded as thin layers of epithelial material which originated from the depressions of the papillae. In these bars, the epithelium has already assumed its normal orientation and state; above, one can observe granulation and light cornification occurring at the tops of the papillae. The free panels constitute the tissue substances which form at the upper part of the damaged papillae. Next, the border between the top of the papillae and the cells located above is scarcely discernable. The cells themselves consist of epithelium with large vacuoles and white blood cells laying between thin amorphous masses. The upper section of this area does not constitute a homogenous, smooth surface. Rather, the cell substances originating from the tops of the papillae are prominent above the normal epithelial surface. As a result of this, the surface covering of these areas still exhibits a macroscopically detectable, irregular, uneven appearance.

In the fourth or convalescent stage, the symptoms of inflammation have for the most part disappeared. Also, above the papillae, epithelium free from white blood cells begins to form. As a result, the epithelium again possesses its normal, uniform appearance. In the Strata lucidum and corneum, one can still see decomposed white blood cells either isolated or in clumps. In this area, when the process has spread up to the papillae themselves, the papillae were found to shrink after recovery. In these cases, the diseased areas then lay somewhat below the intact surrounding tissues. During stages 2 and 3, one finds among the cells of the diseased area that lie near the surface, microorganisms of various

slip (chain and single rods, cocci, particularly streptococci) when the tissues are stained with methenylin-eosin, fuchsin, and methylene blue. Similar microorganisms have been found, as expected, in the mucous membrane tissues from normal cows on numerous occasions. As a result, these findings do not have any of importance.

Nature of the Disease

By means of the successful transmission of the disease from spontaneously ill cattle to calves, which had been kept in a far distant barn and fed unobtainable food and water, as well as through the successful transmission of the disease to additional cattle using infectious materials and blood from the calves, it was proven that the disease is contagious and that the infectious agent can be found in the blood. As already explained above, it must be concluded from the one positive transmission attempt that the infectious agent belongs to the filterable group. With that it is also agreed that with none of the ill animals was it possible to demonstrate a microorganism which could be considered to be the infectious agent using the investigative methods employed.

The disease erupted after an average incubation time of two weeks during our studies. It is clinically characterized as a feverless stomatitis which leads to the formation of small nodules with red margins. There is no destruction of the general state of health of the animal. The nodules can run together and form larger nodules. The nodules, which can appear on all parts of the mucous membrane of the mouth and on the nasal passages, are, first of all, red like their base. Later they take on a yellow to grayish color. We have never observed the formation of pustules and blisters. In later stages of the illness, the affected epithelium is lost. Consequently, sharply demarcated, usually round cavities appear in the centers of the nodules. The

bases of the cavities are lightly granulated and have a different color as compared to the mucous membrane. When the mucous membrane is pink-red in color, the base of the cavity will have a more red color. In the case of a dark-grey mucous membrane, the base will be more darkly colored. During these stages, the diseased area grows out from the periphery. Later, the epithelium proliferates rapidly on and between the papillae of the mucous membrane of the tongue. The newly formed epithelium exhibits a yellowish color due to the deterioration of white blood cells as demonstrated in the histological investigations. Ultimately, about the eighth day after appearance of the nodules, healing begins as a result of normal epithelium formation. The formation of new epithelium tissue commences simultaneously in the centers and on the edges of the erosions. The epidermal-covered areas, which have a dull red color, soon expand so that after a week or so, small areas with a new epithelial covering appear. These areas can be distinguished from the surrounding tissue on the basis of the increased redness and roughness. Both of these symptoms disappear almost completely after a month. In the case of deep-seated lesions, the healing process is delayed quite significantly. In these cases and as a result of often occurring relapses, the illness can persist for months.

During the time that lesions are present in the oral cavity, the animal usually exhibits few additional symptoms of the disease. Whether scab formation on the skin, which was observed with only a few study animals, should be considered to be a symptom of the disease, must be determined by additional investigations. In the case of the animals observed by us, neither temperature elevation, loss of appetite, nor alteration in salivation was observed. Only in the case of very ill animals was the general state of health somewhat impaired. In these cases, the hair covering was shaggy and a foul odor from the oral cavity was noticeable.

The histological study of the diseased areas of the mucous membrane of the mouth showed that the nodule-forming elevations were composed of exudative

inflammations which were restricted to several papillae and small papillary groups. The disease process anatomically was very similar to papular inflammation of the epidermis - eczema papulosum. As a result, we have proposed the designation Stomatitis papulosa infectiosa of cattle for this disease.

After an inspection of the literature, we believe firstly that the disease has not yet been described. It was called to our attention, however, that a report in the Proceedings of the Seventh International Veterinary Congress at Berlin described a similar disease. Professor Hess in his reference concerning the control of hoof-and-mouth disease described a peculiar eruption which could be confused with the contagious disease we have been concerned with. He carried out the following investigations with regards to this other disease:

" A peculiar eruption, which appears on barn and grazing animals, and is possibly identical to the "blister eruptions mentioned in the literature syn. aphthous sporadic flaps", may occur in the form of benign flaps. The disease affects cattle and calves and begins with an easily recognizable loss of appetite and insignificantly increased foaming. In the mouth of the animals, there is a slightly increased temperature, some sensitivity, and reddening in places. In older cases, there is a yellowish discoloration of the mucous membrane of the mouth and distinct swelling of the papillae. In very fresh cases, one finds on the tip of the tongue and in very extensive amounts on the mucous membrane of the mouth, on on the edges of the lip, hempseed- to pea-sized, bright red or yellow nodules which have a small grey, rapidly bursting blister in their center. After bursting are always formed small, lintel- to pea-sized, more or less numerous, lightly running together, and then becoming at the most, five-franc sized, slightly painful, always superficial abscesses of the mucous membrane (eruption). The abscesses can be observed in the nares, on the sides

of the nose, and on the muzzle. In these areas, there is a great deal of similarity to the abscesses associated with malignant catarrh. The abscesses are very quickly covered with a brownish scab. In addition, abscesses are found on the mouth-side of the lower lip, on the toothless edge of the upper jaw, on the edges and corners of the lips, on the buccal mucous membrane, in the throat, on the tip of the tongue, and near to and in front of the ligaments of the tongue. Fresh abscesses have a red surface with a yellowish, cheesy covering and bright or blue-red, swollen, sharp edges. In the case of old abscesses, the surface is yellowish, dry, inflamed, and is raised above the healthy surrounding tissue. Healing of the erosions takes place with five to eight days leaving behind small, isolated or diffuse, yellow, rough, blue-red or yellow patches, or small, very slightly raised, yellow, rough, dry epithelial proliferations. The general state of health is not impaired. The animal shows neither fever nor a reduction in milk production. The disease always proceeds in a benign manner and there are no after-effects. It is not transmitted to other animals by mouth mucus. There are several properties of this disease which characterize it, namely, the general state of health of the animal never suffers, the back of the tongue and the feet remain normal always, and the characteristic blister observed with hoof-and-mouth disease with subsequent mucous membrane lesions and the typical cicatrization (scarring) are absent. This benign mouth affliction can be anatomically described as a follicular catarrh of the oral mucous membrane. However, the etiology of the disease is not known. The owner considered the presence of ant and worm hill, which are frequently found in grass-poor fields and pastures during later summer, to be the cause of the disease. I believe, however, that this disease must be attributed to noxious agents in the feed which are present in the grass during the summer and in the hay during the winter".

The disease studies and described by us is different from that described by Hess, even entirely disregarding the contagious properties detected by us, in that we have never observed blisters. The designation, "sporadic aphtha", would, therefore, not be suitable for the disease described by us. Since the word, aphtha, denotes in veterinary medicine blisters on the mucous membrane of the mouth, aphthic stomatitis would as a result be synonymous with vesicular stomatitis (Friedberger-Frohner, Handbook of Specialized Pathology and Therapy of Domestic Animals, 6th edition, p. 6). Also, the designation "follicular catarrh of the oral mucous membrane" would not be acceptable if one considers that would be made to "follicular rhinitis". The reason for this is that alterations of the mucous gland, which is diseased in the case of follicular rhinitis, are absent in the case of the disease in question here. Nevertheless, the disease described by Hess agrees with the stomatitis papulosa observed by us in many ways. We assume, therefore, that Hess also observed this disease and he confused two different diseases.

Differential Diagnosis

Stomatitis papulosa infectiosa of cattle can be differentiated from so-called sporadic aphtha and from aphthous fever. Stomatitis papulosa can be distinguished from both diseases by the absence of blisters and pustules. Moreover, it can also be differentiated from aphthous fever in that it involves only the oral cavity and not the skin and hooves.